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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
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ART UNIT	PAPER NUMBER
1634	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/535,414	SHARMA ET AL.	
	Examiner	Art Unit	
	Steven C. Pohnert	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 January 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2,4,5,9,13,16-19,23 and 28-35* is/are pending in the application.

4a) Of the above claim(s) *16-19,23 and 28-35* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2,4,5,9 and 13* is/are rejected.

7)☒ Claim(s) *2,4,5,9 and 13* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *19 May 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/2/2007, 5/1/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Sequence compliance

The application fails to comply with CFR 1.821(c) and (d), which states:

(c) Patent applications which contain disclosures of nucleotide and/or amino acid sequences must contain, as a separate part of the disclosure, a paper or compact disc copy (see § 1.52(e)) disclosing the nucleotide and/or amino acid sequences and associated information using the symbols and format in accordance with the requirements of §§ 1.822 and 1.823. This paper or compact disc copy is referred to elsewhere in this subpart as the "Sequence Listing." Each sequence disclosed must appear separately in the "Sequence Listing." Each sequence set forth in the "Sequence Listing" must be assigned a separate sequence identifier. The sequence identifiers must begin with 1 and increase sequentially by integers. If no sequence is present for a sequence identifier, the code "000" must be used in place of the sequence. The response for the numeric identifier <160> must include the total number of SEQ ID NOs, whether followed by a sequence or by the code "000."

(d)Where the description or claims of a patent application discuss a sequence that is set forth in the "Sequence Listing" in accordance with paragraph (c) of this section, reference must be made to the sequence by use of the sequence identifier, preceded by "SEQ ID NO:" in the text of the description or claims, even if the sequence is also embedded in the text of the description or claims of the patent application.

For example, page 89, the first line, refers to SEQ ID NO 123, however the sequence listing only contains SEQ ID NO 1-501. It is noted that the tables contain numerous SEQ ID NO that correspond to nucleic acid sequence other than the 501 listed in the sequence listing.

It is further noted that the specification contains "Sequence ID 502" on page 166-SEQ ID NO 1495 on page 278 that do not appear to be present in the sequence listing.

It is further noted that the specification teaches SEQ ID NO G6 on page 278. G6 is an improper sequence identifier.

Applicant is required to check the rest of the disclosure for any other nucleic acid

or protein sequences and list them in a sequence listing and identify them with a proper SEQ ID NO.

The specification and sequence listing must be amended to bring it into sequence compliance. **For any response to this office action to be fully compliant, the response has to bring the application in compliance with sequence rules.**

Election/Restrictions

Applicant's election with traverse of group I, claims 2-5, 9 and 13 in the reply filed on 1/22/2008 is acknowledged. The traversal is on the ground(s) that Brennan does not teach or suggest the combination of 351 probes that are claimed. This is not found persuasive because Ahr (Journal of Pathology (2001) volume 195, pages 312-320) teaches low density cancer blot of 588 genes (see page 313, 2nd column, top paragraph). Ahr thus teaches an array of more than 351 oligonucleotides probes, but less than 1000 oligonucleotide probes. The 588 probes of Ahr comprise at least 351 oligonucleotide probes with at least 2 nucleotides complementary to the recited SEQ ID NO.

The requirement is still deemed proper and is therefore made FINAL.

1. Claims 16-19, 23 and 28-35 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 1/22/2008.

Information Disclosure Statement

The IDS of May 1, 2006 has listed 17 foreign patent documents. The disclosure only provided the cover page containing only the abstract for 15 of the 17 foreign patent documents. Only abstracts were considered for these 15 documents, however the full disclosure of WO04112589 and WO0004187 were provided and considered.

Specification

The specification has been amended on 5/1/2006 to present a substitute sequence listing. The specification on 5/19/2005 has been amended to claim priority to PCT/2003/005102.

2. The disclosure is objected to because of the following informalities:

3. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. An example of an embedded hyperlink is on page 40, lines 4-5. Applicant is required to check the rest of the disclosure and delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

4. The specification on page 89 states, "Sequences not available for sequence IDs in Table 1, and corresponding sequence Ids in Table 2 and 4. 298, 301, 305, 307, 312, 317, 318, 319, 320, 332, 333, 334, 336, 340, 341, 342, 343, 344, 345, 346, 347, 348, 349, 350, 351, 352, 353, 354, 355, 356, 357, 358, 359, 367, 372, 375, 376, 377, 379, 385, 392, 393, 404, 437, 439, 440, 443, 444, 445, 449, 455, 457, 465, 466, 467, 468, 470, 486, 498, 501, 511, 514, 516, 517, 520, 522, 528, 531, 535, 547, 548, 549, 550, 551, 552, 553, 554, 555, 556, 557, 558, 559, 573, 584, 604, 608, # 616, 620, 623, 640, 659, 662, 664, 667, 668, 673, 677, 678, 679, 681, 695, 702, 712, 716, 825, 886, 894,

902, 909, 916, 1101, 1108, 1109, 1177, 1187, 1193, 1204, 1220, 1239, 1255, 1256, 1342, 1347, 1354, 1357, 1362, 1363, 1364, 1373, 1375, 1379, 1403, 1404, 1405, 1406, 1413." This statement appears to contradict the sequence listing which contains SEQ ID No 1-501 and the sequences of pages 166 to page 279 of the specification. It is unclear how the Table's can be used to teach the sequences and yet this note states the sequences are not available.

5. The specification teaches on page 92, "Please see the note at the bottom of Table 1. Some sequences are missing." The specification is objected to as it teaches informative probes, then says the sequences are not known. It is unclear how a probe can be informative, if the sequence is not known so as it can be differentiated from other sequences.

6. The specification teaches on page 100 a list of informative probes by clone ID, for example XI-8, however the specification does not teach how this clone ID corresponds to any of the SEQ ID NO recited in the specification or disclosed in the sequence listing.

Appropriate correction is required.

Claim Objections

7. Claims 2, 4-5, 9 and 13 are objected to because of the following informalities: Claim 2 is section (i) recites, " repective." The recitation of "repective appears to be a typographical error and should be amended to recite, "respective." Appropriate correction is required.

Claim Rejections - 35 USC § 112

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

New Matter

9. Claims 2, 4-5, 9 and 13 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This new matter rejection is due to the amendment of the claims in response to restriction of 1/22/2008.

Claim 2 has been amended to require, "any of said 351 oligonucleotides or a combination thereof may be replaced in said set...." The response of 1/22/2008 does not suggest where support for this limitation is provided in the specification. The examiners review and searching of the specification provided support for using fragments of the oligonucleotides, but did not reveal support for the replacing or substituting probes or combination of probes. The claims presented in the amendment of 5/19/2005, suggest the limitation of replacing a probe with a fragment. The replacing of a single probe with a fragment does not suggest replacing multiple probes or the whole set of probes with multiple sequences. The recitation of replacing or substituting is broader than just using a fragment and includes replacing a single probe with multiple sequences, or multiple sequences with a single probe. The specification thus does not

provide support for the idea of replacing probes or combinations of probes. The limitation of replacing probes or combination of probes is new matter.

Written Description

10. Claims 2, 4-5, 9 and 13 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The rejected claims 2, 4-5, 9 and 13 encompasses a set of 351 oligonucleotide probes, but not more than 1000 oligonucleotides, of the recited SEQ ID NO, their fragments of at least 15 nucleotides in length, a sequence complementary to the sequences, or a functional equivalent such that it hybridizes under conditions of high stringency . The claims set forth the structural requirements that the fragments of the SEQ ID NO be at least 15 nucleotides in length, however the complementary respective nucleotide of functionally equivalent oligonucleotide are not limited by this length requirement. The claims do not set forth any structural limitations of a complement, a functional equivalent, or high stringency hybridization conditions.

When the claims are analyzed in light of the specification, the invention encompasses an enormous number of nucleotide molecules. The specification teaches an oligonucleotide is at least 6 monomers in a polymeric structure (see page 6, lines 29-30). The specification teaches, "the term "complementary sequences" refers to sequences with consecutive complementary bases (ie. T:A, G:C) and which

complementary sequences are therefore able to bind to one another through their complementarity" (see page 7, lines 18-20). Thus a complementary sequence requires 2 consecutive bases that are complementary to the sequence of interest. The specification further teaches, "Hybridizing under high stringency refers to the above conditions in which washing is performed at 2.times.SSC, 65.degree. C. (where SSC=0.15M NaCl, 0.015M sodium citrate, pH 7.2)" (see page 12, lines 19-23). The specification further teaches, "Table 1 derived oligonucleotide and their functional equivalents are considered different oligonucleotides, complementary oligonucleotides are not considered different" (see page 9, lines 10-15). However the specification appears to contradict this definition on page 9 lines 29-35, "functionally equivalent oligonucleotides (or complementary sequences) have sequence identity or will hybridize, as described hereinafter, to a region of the target molecule to which molecule a Table 1 oligonucleotide or a Table 1 derived oligonucleotide or a complementary oligonucleotide binds." Thus the claims read in light of the specification encompass any nucleic acid sequence of at least 6 bases, with at least 2 bases that are complementary to the SEQ ID NO, or any sequence that remains bound 65° C when washed with 2X SSC. Further as the specification appears to define functional equivalents in two ways, the claims are drawn to any nucleic acid sequence that can be defined as functional equivalents.

In analyzing whether the written description requirement is met for genus claims, it is first determined whether a representative number of species have been by full structure. The instant specification teaches the sequences of SEQ ID NO 1, 2, 3, 4, 5,

11, 12, 13, 19, 25, 31, 32, 33, 34, 36, 37, 39, 45, 46, 47, 48, 50, 55, 56, 60, 61, 64, 66, 68, 73, 74, 75, 76, 77, 78, 80, 83, 85, 86, 90, 96, 98, 99, 100, 101, 105, 106, 107, 109, 111, 114, 115, 116, 117, 119, 120, 121, 122, 123, 124, 125, 127, 128, 130, 131, 132, 133, 135, 136, 137, 138, 144, 145, 146, 147, 148, 149, 150, 151, 152, 153, 154, 155, 156, 157, 158, 159, 161, 162, 163, 164, 165, 166, 168, 169, 171, 173, 174, 175, 176, 177, 178, 179, 180, 182, 183, 185, 186, 187, 190, 191, 195, 197, 198, 199, 200, 202, 204, 206, 207, 210, 212, 214, 216, 217, 218, 219, 220, 221, 222, 224, 225, 229, 230, 231, 232, 233, 234, 235, 236, 237, 238, 239, 240, 243, 244, 245, 249, 251, 256, 258, 259, 260, 261, 262, 267, 268, 270, 272, 273, 274, 275, 276, 278, 279, 280, 282, 284, 286, 287, 289, 291, 292, 295, 296, 297, 298, 299, 301, 303, 305, 307, 308, 309, 310, 311, 314, 315, 316, 317, 318, 319, 320, 321, 322, 323, 324, 325, 326, 327, 328, 329, 330, 331, 332, 333, 334, 335, 336, 337, 338, 339, 340, 341, 342, 343, 344, 345, 346, 347, 348, 349, 351, 352, 353, 355, 356, 357, 359, 361, 363, 364, 365, 366, 367, 368, 369, 370, 371, 374, 375, 376, 377, 378, 379, 380, 381, 382, 383, 384, 385, 386, 387, 388, 389, 390, 391, 392, 393, 394, 395, 396, 397, 398, 399, 400, 401, 402, 403, 404, 405, 406, 408, 409, 410, 411, 412, 413, 414, 415, 416, 417, 418, 419, 420, 421, 422, 423, 424, 425, 426, 427, 428, 429, 430, 431, 432, 433, 434, 435, 436, 437, 438, 439, 440, 441, 444, 445, 446, 447, 448, 449, 450, 451, 452, 453, 454, 455, 457, 458, 459, 460, 461, 463, 464, 465, 466, 467, 468, 469, 470, 471, 472, 473, 474, 475, 476, 477, 478, 479, 480, 481, 482, 484, 487, 489, 490, 496, 497, 498, 499 or 501. The specification does not teach any fragments, complements or functionally equivalent oligonucleotides.

Next, it is determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics (e.g. other nucleotide sequences or positions with in a specific gene or nucleic acid), specific features and functional attributes that would distinguish different members of the claimed genus. In the instant case the specification provides the functional limitation the sequence is a fragment, functional equivalent or complement of the recited SEQ ID NO. These functional limitations would be present in any species of the large genus of nucleic acids claimed. The claims read in light of the specification encompass any nucleic acid molecule from 6 nucleotides in length to the entire length of the recited SEQ ID NO or a nucleic acid that has at least 2 oligonucleotides that are complementary to the recited SEQ ID NO, or can broadly be interpreted as being functionally equivalent or capable of hybridizing under stringent conditions. This is an enormous genus of nucleic acids as the recited SEQ ID NO are approximately 500 nucleotides in length and a combination of any 2 consecutive nucleotides would be an enormous number.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.)

The skilled artisan cannot envision the detailed chemical structure of the encompassed nucleic acids regardless of the complexity or simplicity of the method of

isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The nucleic acid itself is required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993), and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. The current situation is a definition of the compound solely based on its functional utility, as a oligonucleotide probe, without any definition of the particular probes claimed.

Finally, University of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1404, 1405 held that:

To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); In re Gosteli, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) (" [T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood, 107 F.3d at 1572, 41 USPQ2d at 1966.

An adequate written description of a DNA, such as the cDNA of the recombinant plasmids and microorganisms of the '525 patent, "requires a precise definition, such as by structure, formula, chemical name, or physical properties," not a mere wish or plan for obtaining the claimed chemical invention. Fiers v. Revel, 984 F.2d 1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993). Accordingly, "an adequate written description of a DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself." Id. at 1170, 25 USPQ2d at 1606.

In the instant application, the provided information regarding nucleic acid that the fragments of the SEQ ID NO be at least 15 nucleotides in length, however the complementary respective nucleotide of functionally equivalent oligonucleotide are not limited by this length requirement, do not constitute an adequate written description of

the broad subject matter of the claims, and so one of skill in the art cannot envision the detailed chemical structure of the nucleic acids encompassed by the claimed probes. Adequate written description requires more than a statement that nucleic acids with a particular quality are part of the invention and reference to a potential method for their identification. The nucleic acid sequence is required.

In conclusion, the limited information provided regarding that the fragments of the SEQ ID NO be at least 15 nucleotides in length, however the complementary respective nucleotide of functionally equivalent oligonucleotide are not limited by this length requirement is not deemed sufficient to reasonably convey to one skilled in the art nucleic acid molecules claimed.

Thus, having considered the breadth of the claims and the provisions of the specification, it is concluded that the specification does not provide adequate written description for the claims.

11. Claims 2, 4-5, 9 and 13 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. This rejection is drawn to the use of the claimed 351 oligonucleotide probes.

There are many factors to be considered when determining whether there is sufficient evidence to support that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is undue. These factors have

been described by the court in re Wands, 8 USPQ2d 1400 (CA FC 1988). Wands states at page 1404,

"Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in the Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention and the breadth of the claims:

The claims are drawn to a set of 351 oligonucleotide probes, but not more than 1000 oligonucleotides, of the recited SEQ ID NO, their fragments of at least 15 nucleotides in length, a sequence complementary to the sequences, or a functional equivalent such that it hybridizes under conditions of high stringency for the detection of a disease.

For the specification to be enabling for the set of oligonucleotide probes claimed, it must teach how to use the probe set for diagnosis of disease.

The amount of direction or guidance and the Presence and absence of working examples.

The specification, "different sets of probes may be used in techniques to prepare gene expression patterns and identify, diagnose or monitor different states, such as diseases, conditions or stages thereof" (see page 1, 1st paragraph).

The specification teaches, "we now describe probes and sets of

probes derived from cells which are not disease cells and which have not contacted disease cells, which correspond to genes which exhibit altered expression in normal versus disease individuals, for use in methods of identifying, diagnosing or monitoring certain conditions, particularly diseases or stages thereof" (see last paragraph page 4 to top of page 5).

The specification teaches in Table 1a a list of probes informative for disease diagnosis (see page 72). It is noted that table 1a does not comprise SEQ ID NO 1, 2, 3, 4, 5, 11, 12, 13, 19, 25, 31, 32, 33, 34, 36, 37, 39, 45, 46, 47, 48, 50, 55, 56, 60, 61, 64, 66, 68, 73, 74, 75, 76, 77, 78, 80, 83, 85, 86, 90, 96, 98, 99, 100, 101, 105, 106, 107, 109, 111, 114, 115, 116, 117, 119, 120, 121, 122, 123, 124, 125, 127, 128, 130, 131, 132, 133, 135, 136, 137, 138, 144, 145, 146, 147, 148, 149, 150, 151, 152, 153, 154, 155, 156, 157, 158, 159, 161, 162, 163, 164, 165, 166, 168, 169, 171, 173, 174, 175, 176, 177, 178, 179, 180, 182, 183, 185, 186, 187, 190, 191, 195, 197, 198, 199, 200, 202, 204, 206, 207, 210, 212, 214, 216, 217, 218, 219, 220, 221, 222, 224, 225, 229, 230, 231, 232, 233, 234, 235, 236, 237, 238, 239, 240, 243, 244, 245, 249, 251, 256, 258, 259, 260, 261, 262, 267, 268, 270, 272, 273, 274, 275, 276, 278, 279, 280, 282, 284, 286, 287, 289, 291, 292, 295, 296, 297, 298, 299, 301, 303, 305, 307, 308, 309, 310, 311, 314, 315, 316, 317, 318, 319, 320, 321, 322, 323, 324, 325, 326, 327, 328, 329, 330, 331, 332, 333, 334, 335, 336, 337, 338, 339, 340, 341, 342, 343, 344, 345, 346, 347, 348, 349, 351, 352, 353, 355, 356, 357, 359, 361, 363, 364, 365, 366, 367, 368, 369, 370, 371. Further the specification does not teach what disease the Table of 1a corresponds to, or if the sequences recited are informative due to increased or

decreased expression. Further the specification does not teach if the entire combination of probes must be have increased expression relative to a healthy individual, or just subset of the probes. Thus it would be unpredictable to use the 351 probes required of claim 2, to diagnosis disease, when the specification does not teach how the expression as detected by the probes is altered or the number of probes with altered expression that is required for diagnosis.

The specification teaches in Table 1b a list of probes informative for disease diagnosis (see page 78). It is noted that table 1b does not comprise SEQ ID NO 1, 2, 3, 4, 5, 11, 12, 13, 19, 25, 31, 32, 33, 34, 36, 37, 39, 45, 46, 47, 48, 50, 55, 56, 60, 61, 64, 66, 68, 73, 74, 75, 76, 77, 78, 80, 83, 85, 86, 90, 96, 98, 99, 100, 101, 105, 106, 107, 109, 111, 114, 115, 116, 117, 119, 120, 121, 122, 123, 124, 125, 127, 128, 130, 131, 132, 133, 135, 136, 137, 138, 144, 145, 146, 147, 148, 149, 150, 151, 152, 153, 154, 155, 156, 157, 158, 159, 161, 162, 163, 164, 165, 166, 168, 169, 171, 173, 174, 175, 176, 177, 178, 179, 180, 182, 183, 185, 186, 187, 190, 191, 195, 197, 198, 199, 200, 202, 204, 206, 207, 210, 212, 214, 216, 217, 218, 219, 220, 221, 222, 224, 225, 229, 230, 231, 232, 233, 234, 235, 236, 237, 238, 239, 240, 243, 244, 245, 249, 251, 256, 258, 259, 260, 261, 262, 267, 268, 270, 272, 273, 274, 275, 276, 278, 279, 280, 282, 284, 286, 287, 289, 291, 292, 295, 296, 297, Further the specification does not teach what disease the Table 1b corresponds to, or if the sequences recited are informative due to increased or decreased expression. Further the specification does not teach if the entire combination of probes must be have increased expression relative to a healthy individual, or just subset of the probes. Thus it would be unpredictable to use

the 351 probes required of claim 2, to diagnosis disease, when the specification does not teach how the expression as detected by the probes is altered or the number of probes with altered expression that is required for diagnosis.

The specification teaches in Table 2a a list of probes informative for disease diagnosis (see page 90). It is noted that table 2b does not comprise SEQ ID NO 1, 2, 3, 4, 5, 11, 12, 13, 19, 25, 31, 32, 33, 34, 36, 37, 39, 45, 46, 47, 48, 50, 55, 56, 60, 64, 66, 68, 73, 74, 75, 76, 78, 80, 83, 85, 86, 90, 96, 98, 99, 100, 101, 105, 106, 107, 109, 111, 114, 115, 116, 117, 119, 120, 121, 122, 123, 124, 125, 127, 128, 130, 131, 132, 133, 135, 136, 137, 138, 144, 145, 146, 147, 148, 149, 150, 151, 152, 153, 154, 155, 156, 157, 158, 159, 161, 162, 163, 164, 165, 166, 168, 169, 171, 173, 174, 175, 176, 177, 178, 179, 180, 182, 183, 185, 186, 187, 190, 191, 195, 197, 198, 199, 200, 202, 204, 206, 207, 210, 212, 214, 216, 217, 218, 219, 220, 221, 222, 224, 225, 229, 230, 231, 232, 233, 234, 235, 236, 237, 238, 239, 240, 243, 244, 245, 249, 251, 256, 258, 259, 260, 261, 262, 267, 268, 270, 272, 273, 274, 275, 276, 278, 279, 280, 282, 284, 286, 287, 289, 291, 292, 295, 296, 297. However it does contain SEQ ID NO 192, 196, 93 and 108. The specification teaches the probes of Table 2a are diagnostic of breast cancer, however it does not teach if sequences recited are informative due to increased or decreased expression. Further the specification does not teach if the entire combination of probes must be have increased expression relative to a healthy individual, or just subset of the probes. Thus it would be unpredictable to use the 351 probes required of claim 2, to diagnosis breast cancer, when the specification does not teach how the expression as detected by the probes is altered or

the number of probes with altered expression that is required for diagnosis. Further as Table 2 appears to require probes that are not in the elected combination it would suggest the claimed combination would not be predictably associated with breast cancer.

Further the specification teaches in Figure 2b (pages 92-99) another set of probes that are diagnostic of breast cancer that appears to comprise the sequences of Table 2a, but includes additional sequences, for example SEQ ID NO 1331 appears to be present in Table 2b, but not table 2a. It would thus be unpredictable to determine which probes are indicative of breast cancer, when the specification teaches 2 different sets of probes that are not coextensive in scope, but both are informative of breast cancer. Thus the skilled artisan would not be able to predictably determine the probes required for detection of breast cancer.

The specification further recites in Table 3 (page 100) of the specification another list of genes informative of breast cancer by clone ID. Table 3 does not teach how the clone ID of the table refer to any sequences in the specification, nor the level of expression required for each of the clones to be informative of breast cancer. Thus it would be unpredictable to use the claimed 351 probes for the detection of breast cancer without guidance on how expression on all or a specific subset of probes must vary to be diagnostic of breast cancer.

The specification teaches in Table 4a list of probes informative for Alzheimer diagnosis (see page 101). It is noted that table 4a does not comprise SEQ ID NO 1, 2, 3, 4, 5, 11, 12, 13, 19, 25, 31, 32, 33, 34, 36, 37, 39, 45, 46, 47, 48, 50, 55, 56, 60, 61,

64, 66, 68, 73, 74, 75, 76, 77, 78, 80, 83, 85, 86, 90, 96, 98, 99, 100, 101, 105, 106, 107, 109, 111, 114, 115, 116, 117, 119, 120, 121, 122, 123, 124, 125, 127, 128, 130, 131, 132, 133, 135, 136, 137, 138, 144, 145, 146, 147, 148, 149, 150, 151, 152, 153, 154, 155, 156, 157, 158, 159, 161, 162, 163, 164, 165, 166, 168, 169, 171, 173, 174, 175, 176, 177, 178, 179, 180, 182, 183, 185, 186, 187, 190, 191, 195, 197, 198, 199, 200, 202, 204, 206, 207, 210, 212, 214, 216, 217, 218, 219, 220, 221, 222, 224, 225, 229, 230, 231, 232, 233, 234, 235, 236, 237, 238, 239, 240, 243, 244, 245, 249, 251, 256, 258, 259, 260, 261, 262, 267, 268, 270, 272, 273, 274, 275, 276, 278, 279, 280, 282, 284, 286, 287, 289, 291, 292, 295, 296, 297, 298, 299, 301, 303, 305, 307, 308, 309, 310, 311, 314, 315, 316, 317, 318, 319, 320, 321, 322, 323, 324, 325, 327, 328, 329, 330, 331, 332, 333, 334, 335, 336, 337, 338, 339, 340, 341, 342, 343, 344, 345, 346, 347, 348, 349, 351, 352, 353, 355, 356, 357, 359, 365, 366, 367, 369, 370, 371. Further the specification does not teach if the probes of Table 4a correspond to sequences informative due to increased or decreased expression. Further the specification does not teach if the entire combination of probes must be have increased or decreased expression relative to a healthy individual, or just subset of the probes. Thus it would be unpredictable to use the 351 probes required of claim 2, to diagnosis of Alzheimers disease, when the specification does not teach how the expression as detected by the probes is altered or the number of probes with altered expression that is required for diagnosis.

The specification further teaches Table 9 as a list of probes that are informative for both Alzheimer's and Breast cancer. It is noted that table 9 does not comprise SEQ

ID NO 1, 2, 3, 4, 5, 11, 12, 13, 19, 25, 31, 32, 33, 34, 36, 37, 39, 45, 46, 47, 48, 50, 55, 56, 60, 61, 64, 66, 68, 73, 74, 75, 76, 77, 78, 80, 83, 85, 86, 90, 96, 98, 99, 100, 101, 105, 106, 107, 109, 111, 114, 115, 116, 117, 119, 120, 121, 122, 123, 124, 125, 127, 128, 130, 131, 132, 133, 135, 136, 137, 138, 144, 145, 146, 147, 148, 149, 150, 151, 152, 153, 154, 155, 156, 157, 158, 159, 161, 162, 163, 164, 165, 166, 168, 169, 171, 173, 174, 175, 176, 177, 178, 179, 180, 182, 183, 185, 186, 187, 190, 191, 195, 197, 198, 199, 200, 202, 204, 206, 207, 210, 212, 214, 216, 217, 218, 219, 220, 221, 222, 224, 225, 229, 230, 231, 232, 233, 234, 235, 236, 237, 238, 239, 240, 243, 244, 245, 249, 251, 256, 258, 259, 260, 261, 262, 267, 268, 270, 272, 273, 274, 275, 276, 278, 279, 280, 282, 284, 286, 287, 289, 291, 292, 295, 296, 297, 298, 299, 301, 303, 305, 307. It would thus be unpredictable to use an array comprising the recited SEQ ID NO for the diagnosis of Alzheimer's or breast cancer, without guidance as to whether all the probes or a subset of probes must demonstrate increase or decreased expression or to determine which disease is present. As the specification and claims are written it appears that the presence of all the sequences of Table 9 identify patients with both Alzheimers and breast cancer.

The state of prior art and the predictability or unpredictability of the art:

The art of Cheung et al (Nature Genetics, 2003, volume 33, pages 422-425) teaches that there is natural variation in gene expression among different individuals. The reference teaches an assessment of natural variation of gene expression in lymphoblastoid cells in humans, and analyzes the variation of expression data among individuals and within individuals (replicates) p.422, last paragraph; Fig 1). The data

indicates that, for example, expression of ACTG2 in 35 individuals varied by a factor of 17; and that in expression of the 40 genes with the highest variance ratios, the highest and lowest values differed by a factor of 2.4 or greater (Fig 3).

The unpredictability of correlating gene expression level to any phenotypic quality is taught in the prior art of Wu (Journal of Pathology, 2001, volume 195, pages 53-65). Wu teaches that gene expression data must be interpreted in the context of other biological knowledge, involving various types of 'post genomics' informatics, including gene networks, gene pathways, and gene ontologies (p.53, left col.). The reference indicates that many factors may be influential to the outcome of data analysis, and teaches that expression data can be interpreted in many ways. The conclusions that can be drawn from a given set of data depend heavily on the particular choice of data analysis. Much of the data analysis depends on such low-level considerations as normalization and such basic assumptions as normality (p.63 - Discussion). The prior art of Newton et al (Journal of Computational Biology, 2001, volume 8, pages 37-52) further teaches the difficulty in applying gene expression results. Newton et al teaches that a basic statistical problem is determining when the measured differential expression is likely to reflect a real biological shift in gene expression, and replication of data is critical to validation (p.38, third full paragraph).

The level of skill in the art:

The level of skill in the art is deemed to be high.

Quantity of experimentation necessary:

In order to practice the invention as claimed, one would first have to establish that a predicative relationship exists between the claimed array and disease diagnosis in a subject. This would be replete with unpredictable trial and error analysis because the specification does not how the expressed probe set is used to diagnose disease. Specifically the specification has in tables 1a, 1b, 2a, 2 b, 4 and 9 of the specification identify sequences that are informative of a disease state, breast cancer, Alzheimer's or Alzheimer's and breast cancer, however the specification does not teach how the combination of SEQ ID NO diagnose Alzheimer's or breast cancer. Thus the skilled artisan would have to determine if all the claimed capture probes or a specific subcombination of probes would have to demonstrate an increase or decrease expression to result in the diagnosis of any disease or Alzheimer's or breast cancer. This would be further unpredictable as the various tables do not recite that the claimed genes are informative. Specifically the table 2, does not comprise claimed SEQ ID NO 1, 2, 3, 4, 5, 11, 12, 13, 19, 25, 31, 32, 33, 34, 36, 37, 39, 45, 46, 47, 48, 50, 55, 56, 60, 64, 66, 68, 73, 74, 75, 76, 78, 80, 83, 85, 86, 90, 96, 98, 99, 100, 101, 105, 106, 107, 109, 111, 114, 115, 116, 117, 119, 120, 121, 122, 123, 124, 125, 127, 128, 130, 131, 132, 133, 135, 136, 137, 138, 144, 145, 146, 147, 148, 149, 150, 151, 152, 153, 154, 155, 156, 157, 158, 159, 161, 162, 163, 164, 165, 166, 168, 169, 171, 173, 174, 175, 176, 177, 178, 179, 180, 182, 183, 185, 186, 187, 190, 191, 195, 197, 198, 199, 200, 202, 204, 206, 207, 210, 212, 214, 216, 217, 218, 219, 220, 221, 222, 224, 225, 229, 230, 231, 232, 233, 234, 235, 236, 237, 238, 239, 240, 243, 244, 245, 249, 251, 256, 258, 259, 260, 261, 262, 267, 268, 270, 272, 273, 274, 275, 276, 278, 279, 280, 282,

284, 286, 287, 289, 291, 292, 295, 296, 297. The tables that refer to the same diseases such as 2a and 2b; 4a and 4b teach different combinations of SEQ ID NO, and thus suggest that the combination of probes are not predictably associated with disease. Thus the skilled artisan would have to undertake unpredictable trial and error experimentation to determine which combination of SEQ ID No are predictive of a disease state.

Wu, Newton and Cheung teach that gene expression analysis is variable within a subject between samples. It would thus be unpredictable to associate the findings of a single study with diagnosis of a disease without specific guidance on the level of increased or decreased expression required. It would further be unpredictable without guidance as to the nucleic acid sequences or combination of nucleic acid sequences that must identified by expression level as indicative for diagnosis.

Therefor, in light of the breadth of the claims, the lack of guidance in the specification, the high level of unpredictability in the associated technology, the nature of the invention, the negative teachings in the art, and the quantity of unpredictable experimentation necessary to practice the claimed invention, it would require undue experimentation to practice the invention as claimed.

Claim Rejections - 35 USC § 102

12. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

13. Claims 2, 4, 9, and 13 are rejected under 35 U.S.C. 102(b) as being anticipated by Ahr et al (Journal of Pathology (2001) volume 195, pages 312-320).

This rejection is presented to the breadth of the composition claimed oligonucleotide probe set. This rejection does not contradict the enablement rejection as it is directed to the structural limitations of the claims.

Claims 2, 4, 9 and 13 are drawn to a set of 351 oligonucleotide probes, but not more than 1000 oligonucleotides, of the recited SEQ ID NO, their fragments of at least 15 nucleotides in length, a sequence complementary to the sequences, or a functional equivalent such that it hybridizes under conditions of high stringency. The recitation of a complementary sequence or functional equivalent does not contain the length requirement. The specification teaches, "the term "complementary sequences" refers to sequences with consecutive complementary bases (ie. T:A, G:C) and which complementary sequences are therefore able to bind to one another through their complementarity" (see page 7, lines 18-20)." The specification further teaches, "Table 1 derived oligonucleotide and their functional equivalents are considered different oligonucleotides, complementary oligonucleotides are not considered different" (see page 9, lines 10-15). However the specification appears to contradict this definition on page 9 lines 29-35, "functionally equivalent oligonucleotides (or complementary sequences) have sequence identity or will hybridize, as described hereinafter, to a region of the target molecule to which molecule a Table 1 oligonucleotide or a Table 1

derived oligonucleotide or a complementary oligonucleotide binds." The claims thus broadly require at least 351 oligonucleotide probes, but not more than 1000 probes that have at least 2 consecutive nucleotides that are complementary to the recited SEQ ID NO.

With respect to claims 2, 4, 9, and 13, Ahr teaches low density cancer blot of 588 genes (see page 313, 2nd column, top paragraph). The 588 probes of Ahr thus contain at leat 351 probes that have 2 nucleotides that are complementary to the recited SEQ ID NO. Ahr thus teaches an array of more than 351 oligonucleotides probes, but less than 1000 oligonucleotide probes. The 588 probes of Ahr comprise at least 351 oligonucleotide probes with at least 2 nucleotides complementary to the recited SEQ ID NO and anticipate the instant claims.

Summary

No claims are allowed.

Conclusions

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Steven C. Pohnert whose telephone number is 571-272-3803. The examiner can normally be reached on Monday-Friday 6:30-4:00, second Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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